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Original Article

Association between statewide adoption of the CDC's Core Elements of Hospital Antimicrobial Stewardship Programs and rates of methicillin-resistant *Staphylococcus aureus* bacteremia and *Clostridioides difficile* infection in the United States

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Abstract

Objective: To measure the association between statewide adoption of the Centers for Disease Control and Prevention's (CDC's) Core Elements for Hospital Antimicrobial Stewardship Programs (Core Elements) and hospital-associated methicillin-resistant Staphylococcus aureus bacteremia (MRSA) and Clostridioides difficile infection (CDI) rates in the United States. We hypothesized that states with a higher percentage of reported compliance with the Core Elements have significantly lower MRSA and CDI rates.

Participants: All US states.

Design: Observational longitudinal study.

Methods: We used 2014–2016 data from Hospital Compare, Provider of Service files, Medicare cost reports, and the CDC's Patient Safety Atlas website. Outcomes were MRSA standardized infection ratio (SIR) and CDI SIR. The key explanatory variable was the percentage of hospitals that meet the Core Elements in each state. We estimated state and time fixed-effects models with time-variant controls, and we weighted our analyses for the number of hospitals in the state.

Results: The percentage of hospitals reporting compliance with the Core Elements between 2014 and 2016 increased in all states. A 1% increase in reported ASP compliance was associated with a 0.3% decrease ($P < .01$) in CDIs in 2016 relative to 2014. We did not find an association for MRSA infections.

Conclusions: Increasing documentation of the Core Elements may be associated with decreases in the CDI SIR. We did not find evidence of such an association for the MRSA SIR, probably due to the short length of the study and variety of stewardship strategies that ASPs may encompass.

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Antimicrobial resistance (AMR) is a major public health threat at the intersection of healthcare quality and global health security.[1,2] In the United States in 2013, AMR contributed to 23,000 deaths, with an estimated $20 billion in direct healthcare costs and $35 billion in overall societal costs.[2] Misuse and overuse of antimicrobials are major causes of AMR, such as methicillin-resistant *Staphylococcus aureus* bacteremia (MRSA). An important opportunity exists to reduce the incidence and impact of AMR because up to 50% of all antimicrobials prescribed in US acute-care hospitals are unnecessary or inappropriate.[3–5] Beyond resistance, incorrect antibiotic prescribing can increase adverse events (sometimes severe) and leads to ~250,000 *Clostridioides difficile* infections (CDIs) in hospitalized patients every year,[2] with no therapeutic benefit.[4,6]

Antimicrobial stewardship programs (ASPs) can help ensure that antimicrobials are only prescribed when needed and that the right antimicrobial, dose, and duration of treatment are being prescribed.[7] Although ASPs can take different approaches (eg, antibiotic time outs, prior authorization, and prospective audit and feedback), all involve stricter assessment and monitoring of antimicrobial use, sometimes restricting the use of broad-spectrum agents.[7,8] A growing body of evidence has shown that ASPs can optimize antimicrobial use,[9,10] reduce adverse events[9] and

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resistance rates,[11] all of which improve quality of care and patient safety. Reduced antimicrobial use has not been shown to negatively affect, and may improve, patient outcomes.[12] Most ASP literature focuses on prescribing practices or antimicrobial use[8,10,13] rather than resistance rates. Moreover, most studies in which the impact of ASP on infection rates was assessed were conducted in a single and/or international setting, so external generalizability was compromised.[14]

In 2014, the CDC launched the Core Elements for Hospital Antimicrobial Stewardship Programs (hereafter, Core Elements), specific guidelines for ASPs in acute-care hospitals and other healthcare settings[7] that added to previous work of the Society for Healthcare Epidemiology of America, Infectious Disease Society of America, and The Joint Commission.[7,15] The CDC guidelines set a minimum standard for hospitals with 7 core elements for ASPs: leadership commitment, accountability, drug expertise, action, tracking, reporting, and education.[7]

Despite the CDC guidelines for a minimum standard ASP and its assessment in hospitals, the effect of the Core Elements on resistance rates and CDI remains unclear. Furthermore, the impact of ASPs on actual AMR rates in hospitals is uncertain or has not been explored. The objective of this study was to examine reported compliance with the Core Elements between 2014 and 2016, as well as the association between statewide adoption of the Core Elements and hospital MRSA and CDI rates in all US states. We formulated the following hypotheses: (1) that reported compliance with the Core Elements would increase between 2014 and 2016 and (2) that states with higher percentages of reported compliance to the Core Elements would have significantly lower MRSA and CDI rates.

Methods

Data sources

We merged 2014–2017 hospital-level data from the Centers for Medicare & Medicaid Services' (CMS) Hospital Compare data, Provider of Service files, Medicare cost reports, and 2014–2016 state-level data from the CDC's Patient Safety Atlas website. Hospital Compare compiles quality of care information from >4,000 Medicare-certified hospitals; Provider of Service files contain data on hospital characteristics and type of services provided; and Medicare cost reports include utilization and cost data in addition to facility characteristics regarding all Medicare-certified providers. The CDC's Patient Safety Atlas website provides access to state-level data on hospital-acquired infections, antimicrobial resistance, and ASPs from acute-care hospitals nationwide, collected through the CDC National Healthcare Safety Network (NHSN) Patient Safety Component Annual Hospital Survey. The ASP data are used to assess whether facilities (reportedly) meet the criteria for each of the 7 recommended core elements.

Participants

The study population included all 50 US states plus the District of Columbia from 2014 to 2016. Medicare and Hospital Compare data were originally compiled at the hospital level and were collapsed at the state level using hospital size weights (ie, number of beds). These data included all Medicare-certified acute-care hospitals in the United States for which MRSA and CDI standardized infection ratio (SIR) data were available for 2014–2016 (ie, a large proportion of the total acute-care hospitals in the United States). Veterans' Affairs (VA), children's, and critical-access hospitals were excluded because of different data collection periods, different case mixes and different hospital epidemiology, and lack of reporting requirements for infection data, respectively.

Similarly, for ASP data, 4,173 to 4,764 acute-care facilities completed the NHSN survey from 2014 to 2016, respectively,[16] although critical-access hospitals may be underrepresented due to reporting requirements. The total number of acute-care hospitals in the United States is 5,262,[17] and the percentage of facilities that reported ASP data to NHSN was ~79.3%–90.5% during the study years, which should largely overlap with hospitals in the Medicare/Hospital Compare data set.

Measures

Table 1 contains operational definitions for each variable. We defined our 2 outcomes as follows: the MRSA SIR is the ratio of MRSA bacteremia laboratory-identified events to the predicted number of MRSA bacteremia events, and the CDI SIR is the ratio of CDI laboratory-identified events to the predicted number of CDI events. SIRs are calculated for each hospital by the NHSN and are made available through the Hospital Compare data system. MRSA and CDI predicted events are calculated by the NHSN based on several predictors, which are described in Table 1. Notably, MRSA and CDI SIRs are calculated only for hospitals with at least 1 predicted event.[18]

Our main regressor is the percentage of hospitals that reported complying with the Core Elements in a given state over time (2014–2016). The CDC's Patient Safety Atlas website shows a substantial increase in the percentage of reported compliance in every state nationwide from 2014 to 2016.[16] Time-variant independent variables in the models included the following: type of ownership, emergency services, intensive care unit (ICU) services, medical school affiliation, bed count, quality accreditation, number of changes in ownership, compliance with CMS requirements, % ICU beds, average length of stay, patient safety index, and 30-day readmission rate.

Analysis

First, we used descriptive statistics to measure state-level variation in the percentage of hospitals meeting the Core Elements between 2014 and 2016. Then, for each outcome, we estimated a set of different models using state fixed effects.

We chose state fixed effects because several time-invariant unmeasured confounders affect the relationship between ASP and resistance and/or CDI rates: location (state, rural, vs urban), hospital ownership, teaching status, specialty hospital, patient case mix and structural factors. Because most of these variables had not been observed, we were not able to verify whether they were truly time invariant, but we assumed that they had very little variation, if any.

We used state-level analyses due to the availability of ASP data only at the state level; thus, hospital data were aggregated at the state level and were weighted using hospital size (ie, number of beds). The analyses were also weighted by number of hospitals in each state, and we controlled for the time-variant characteristics listed in Table 1. In terms of model specification, the results of a Hausman test indicated a preference for the fixed-effects model over a random-effects model.

We also tested our model using a lagged explanatory variable (2014–2016 ASP data and 2015–2017 outcomes) to address a possible reverse causation in states that improved the ASP because they already had high rates of AMR, and an interaction between ASP and time (years) to test whether there could be differential

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Table 1. Data Sources and Variables, 2014–2017

Variable	Description	Source
Outcomes		
MRSA SIR	MRSA standardized infection ratio: no. observed MRSA bacteremia (laboratory-identified) divided by predicted no. MRSA in the hospital within a year. MRSA predicted events are calculated based on admission prevalence rate of MRSA infections, average length of stay, medical school affiliation, type of hospital, number of ICU beds, MRSA infections identified in the emergency department and/or observation units	Hospital Compare
CDI SIR	CDI standardized infection ratio: no. observed CDIs (laboratory-identified) divided by predicted no. CDIs in the hospital within a year. Predicted CDIs are calculated using type of laboratory test used to identify CDI, whether the hospital has emergency departments and/or observation units that collect stool specimens for CDI testing, facility bed size, no. of ICU beds, medical school affiliation, admission prevalence rate of CDI, and type of hospital.	Hospital Compare
Explanatory variable		
ASP compliance	% of hospitals that meet the CDC's Core Elements for Antimicrobial Stewardship Programs within a given state	CDC Patient Safety Atlas
Control variables		
Hospital ownership	Categorical variable for public, private for-profit, and private not-for-profit (referent category)	Hospital Compare
Rural	Dichotomous variable for whether the hospital is in a rural area (=1; 0 otherwise)	CMS Provider of Service file
Emergency services	Dichotomous variable for whether the hospital provides emergency services (=1; 0 otherwise)	Hospital Compare
ICU services	Dichotomous variable for whether the hospital provides intensive care services (=1; 0 otherwise)	CMS Provider of Service file
Teaching hospital	Dichotomous variable for whether the hospital is affiliated with a medical school (=1; 0 otherwise)	CMS Provider of Service file
Hospital size	No. of beds in the hospital	Medicare Cost reports
No. of changes in ownership	No. of times hospital has undergone a change in ownership. Categorical variable for "No changes" (=1), "One time" (=2), "Two or more" (=3) changes in ownership within a given year.	CMS Provider of Service file
Share of critically ill patients	% ICU beds in the hospital	Medicare Cost reports
Quality accreditation	Dichotomous variable for whether the hospital is accredited by a CMS-approved accreditation organization (=1; 0 otherwise). Quality accreditation organizations include The Joint Commission (most of accredited hospitals), American Osteopathic Association Healthcare Facilities Accreditation Program, Det Norske Veritas Germanischer Lloyd, and Center for Improvement in Healthcare Quality	CMS Provider of Service file
Compliance with CMS requirements	Dichotomous variable for whether the hospital is in compliance with Medicare Conditions of Participation (CoP) for all services, areas, and locations covered by the hospital's provider agreement under its CMS certification no. (=1; 0 otherwise)	CMS Provider of Service file
Length of stay	Mean length of inpatient stay in days	Medicare Cost reports
Patient safety index	Composite measure of rates of pressure ulcer, iatrogenic pneumothorax, in-hospital fall with hip fracture, perioperative hemorrhage or hematoma, postoperative acute kidney injury, postoperative respiratory failure, perioperative pulmonary embolism or deep vein thrombosis, postoperative sepsis, postoperative wound dehiscence and unrecognized abdominopelvic accidental puncture/laceration. Includes Medicare beneficiaries only and is adjusted for patient characteristics. Data collected bi-yearly from July to June.	Hospital Compare
30-d readmission rate	% patients readmitted to the hospital within 30 d of discharge. Includes Medicare beneficiaries only and is adjusted for patient characteristics. Data collected yearly from July to June.	Hospital Compare

Note. MRSA, methicillin-resistant *Staphylococcus aureus*; SIR, standardized infection ratio; CDI, *Clostridioides difficile* infection; ASP, antimicrobial stewardship program; CMS, Centers for Medicare & Medicaid Services; ICU, intensive care unit.

treatment effects at each specific year. Moreover, we re-estimated the models using hospital-level data, even though ASP variation occurred only at the state level.

Results

The average reported ASP compliance across states from 2014 to 2016 was 48.1% (Table 2). Increases in the percentage of hospitals that reported complying with the Core Elements guidelines between 2014 and 2016 ranged from 6% to 62% (Fig. 1). States with a smaller absolute increase usually had a higher percentage in 2014. For example, states that reported ≥50% compliance in 2014 (eg, Arizona, California, Idaho, Massachusetts, Maine, and Utah) had only 6%–26% increases in ASP compliance by 2016. Similarly, states that reported only ≤29% compliance in 2014 (eg, Connecticut, District of Columbia, Hawaii, Tennessee, and West Virginia) had the highest absolute increases in percentage of hospitals meeting the 7 core elements (36%–62%).

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Table 2. Descriptive Statistics for MRSA and CDI Models, 2014–2016

Variable	US States, 2014–2016, (n = 153) Mean (SD) or %
MRSA SIR	0.87 (0.29)
CDI SIR	0.91 (0.14)
% ASP compliance in the state	48.1 (17.5)
Public, %	14.0
Private for profit, %	14.4
Private not for profit, %	71.6
Teaching, %	55.5
Rural, %	17.5
Bed count	410 (126)
Quality Accredited, %	94.5
Changes in ownership = 0, %	32.0
Changes in ownership = 1, %	28.4
Changes in ownership >1, %	39.6
Compliant CMS requirements, %	71.9
Emergency services, %	98.1
% ICU beds	7.6 (1.5)
Length of stay, d	3.6 (0.4)
ICU services, %	92.1
Patient safety index	0.92 (0.1)
% Hospital readmissions	15.3 (0.6)

Note, MRSA, methicillin-resistant *Staphylococcus aureus*; CDI, *Clostridioides difficile* infection; SIR, standardized infection ratio; CMS, Centers for Medicare & Medicaid Services; ICU, intensive care unit.

We hypothesized that states with a higher percentage of reported compliance with the Core Elements guidelines would have significantly lower MRSA and CDI rates. Our findings do not support our hypothesis for MRSA (Table 3). However, we found support for our hypothesis in the CDI model in which reported ASP compliance was interacted with year. A 1% increase in reported ASP compliance was associated with a 0.3% decrease ($P < .01$) in CDI in 2016 relative to 2014 (Table 4). This result suggests a differential treatment effect of increasing ASP compliance at the state level across years.

We did not find evidence of a lagged effect (or reverse causation) of reported ASP compliance in any of the models. Our results in the MRSA and CDI models were consistent in both state-level and hospital-level analyses.

Discussion

ASPs that encourage compliance with the 7 Core Elements have the potential to reduce AMR. In our study of all US states, we tested 2 hypotheses: (1) reported compliance with the Core Elements would increase between 2014 and 2016 and (2) states with a higher percentage of reported compliance with the Core Elements guidelines would have significantly lower MRSA and CDI rates. Our results show that reported compliance with the Core Elements increased nationwide and was associated with a decrease in CDIs. However, we did not find this association for MRSA infections.

Increased reported compliance with the Core Elements

As hypothesized, reported compliance with the Core Elements increased in every US state from 2014 to 2016. Nationally, the proportion of hospitals that met the 7 core components increased

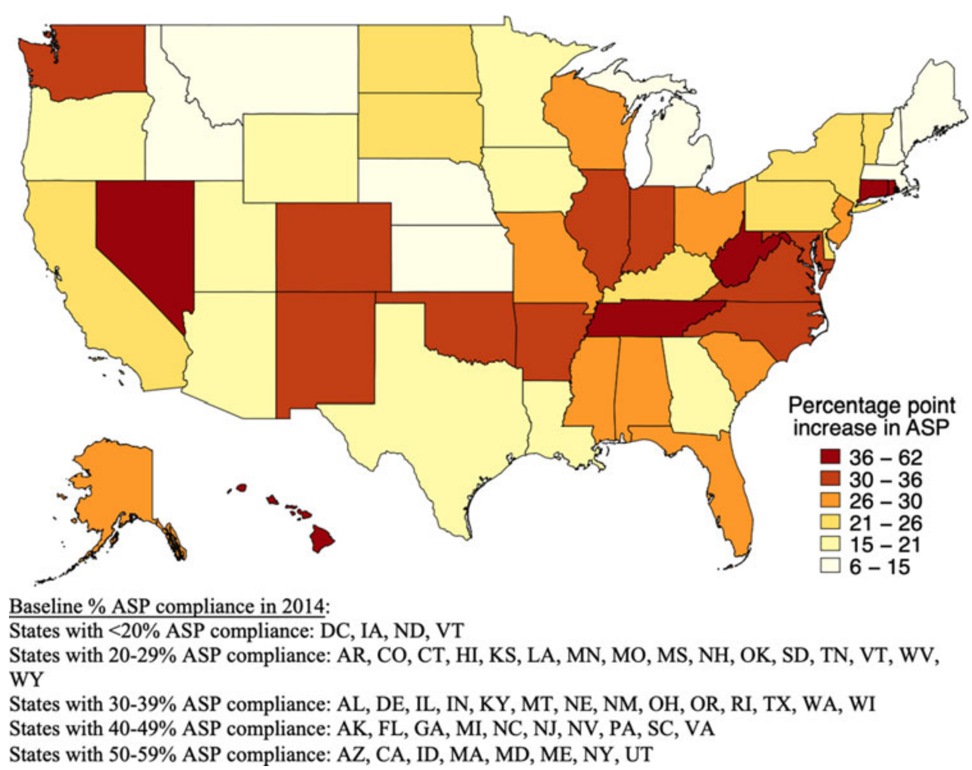

Fig. 1. Increase in antimicrobial stewardship programs (ASPs) meeting the CDC's Core Elements for Hospital Antimicrobial Stewardship in US states, 2014–2016.

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Table 3. Regression-Adjusted Estimates for the Association Between % ASPs Meeting the CDC's Core Elements of Hospital Antimicrobial Stewardship and MRSA SIRs, 2014–2017

MRSA Models	Initial Model	Initial Model With Interactions Between ASP and Year	Initial Model With Lagged ASP
Variable	*b* (SE)[a]	*b* (SE)	*b* (SE)
% ASP compliance	0 (0.002)	−0.001 (0.003)	
2015	0.075 (0.058)	0.002 (0.13)	
2016	0.098 (0.078)	0.05 (0.152)	−0.04 (0.041)
% ASP × 2015[b]		0.002 (0.002)	
% ASP × 2016[c]		0.001 (0.003)	
Teaching	0.003 (0.648)	0.105 (0.636)	0.509 (0.737)
Bed count	−0.002 (0.002)	−0.003 (0.003)	0 (0.003)
Quality accredited	−0.486 (0.354)	−0.463 (0.369)	0.24 (0.47)
Compliant with CMS requirements	−0.311 (0.514)	−0.339 (0.507)	−0.307 (0.502)
% ICU beds	−0.054 (0.063)	−0.059 (0.06)	−0.029 (0.048)
Length of stay	0.134 (0.312)	0.109 (0.304)	−0.149 (0.15)
Patient safety index	−0.161 (0.285)	−0.126 (0.286)	−0.289 (0.249)
% Hospital readmissions	0.209 (0.115)	0.223 (0.123)	0.025 (0.096)
Lagged % ASP[d]			0.001 (0.002)
2017			−0.153 (0.07)*
Public	−0.605 (1.087)	−0.488 (1.03)	1.528 (0.439)**
Private for profit	1.13 (0.632)	1.097 (0.659)	1.912 (0.965)
Rural	0.062 (0.737)	−0.085 (0.656)	−0.258 (0.448)
Changes in ownership = 1	1.78 (1.412)	1.815 (1.467)	−0.369 (0.763)
Changes in ownership >1	−0.998 (1.929)	−0.984 (1.954)	−1.348 (1.343)
Emergency services	0.749 (1.007)	0.748 (1.019)	−0.371 (0.5)
ICU services	−1.488 (1.516)	−1.198 (1.469)	0.247 (0.578)
Constant	−0.26 (2.982)	−0.422 (3.114)	1.453 (2.157)
N	151	151	152
R^2	0.392	0.397	0.484

Note. ASP, antimicrobial stewardship program; MRSA, methicillin-resistant *Staphylococcus aureus*; SIR, standardized infection ratio; CMS, Centers for Medicare and Medicaid Services; ICU, intensive care unit; SE, standard error.
*$P < .05$; **$P < .01$.
[a]*b* = regression coefficient, the effect of a 1-unit increase in the independent variable on MRSA SIR.
[b]Effect of ASP in 2015, relative to 2014.
[c]Effect of ASP in 2016, relative to 2014.
[d]Effect of ASP on MRSA in the following year.

from 39% in 2014[19] to 48% in 2015[20] and 64% in 2016.[16] Not surprisingly, increases in reported compliance were greater in states with lower compliance in the initial study period. Increases may have resulted from recent national policies that encourage ASPs to be implemented in all healthcare facilities, such as the National Action Plan for combating Antibiotic Resistance,[21] the ASP Guidelines by the Society for Healthcare Epidemiology of America (SHEA),[22] and The Joint Commission Standards for Antimicrobial Stewardship.[15,23]

Despite nationwide increases in reported ASP adoption, we observed regional differences in reported compliance. States with a higher percentage of compliance were closer to the west or east coast compared to states in the center of the country.[20] Studies that had access to more granular data were able to identify that larger hospitals (ie, >200 beds) and teaching hospitals were more likely to report that all 7 core elements were implemented,[20,24,25] which may also explain the underrepresentation of smaller facilities (eg, critical-access hospitals) in hospital-reported surveys. The core element "action" was the most commonly implemented, although that could encompass a range of different facility-specific activities. The "leadership commitment" element (eg, written support from administrators and ASP-related compensation) was the strongest predictor for a hospital meeting the 7 core elements.[20,25]

Implementing all 7 of the core elements has been associated with a decrease in antimicrobial use up to 10% in a large healthcare system,[26] but an ideal level of antimicrobial use in hospitals is not known. However, the decrease in antimicrobial use can certainly improve antimicrobial-related adverse events. With national support and local implementation of stewardship activities, the judicious use of antimicrobials can be achieved, and emergence of resistance can be contained.

ASP association with decreased CDIs

As hypothesized, reported ASP compliance with the Core Elements guidelines was associated with a significant decrease in CDI SIR in 2016 relative to 2014. This significant association in 2016 may be related to the recent increase in ASP compliance; reported ASP compliance increased in every state from 2014 onward.

This finding is consistent with previous studies conducted in single hospital settings.[14,27,28] The VA system also reported declining CDI rates after implementing national stewardship activities.[13] A reduction in CDI has been associated with decreased antibiotic prescribing in outpatient settings as well.[29,30] Restrictive and persuasive (eg, audit and feedback) stewardship strategies were found to be more effective in decreasing CDI rates.[14,30,31]

Moreover, ASPs may sometimes include disease-specific policies, such as guidelines for treatment of CDI, which recommend stopping unnecessary antimicrobials for any patient with CDI.[7,32] Better clinical response and reduced risk of recurrence follow as a result[32] and may also explain the association between ASP and reduced CDI rates in this study. In summary, our study results are consistent with evidence from single settings and other healthcare venues.

No effect on MRSA infections

Our hypothesis was not supported for MRSA infections. Our study did not find evidence of an association between reported ASP and MRSA. There are several possible explanations for this difference. First, ASP efforts may not equally impact

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Table 4. Regression-Adjusted Estimates for the Association Between % ASPs Meeting the CDC's Core Elements of Hospital Antimicrobial Stewardship and CDI SIRs, 2014–2017

CDI Models	Initial Model	Initial Model With Interactions Between ASP and Year	Initial Model With Lagged ASP
Variable	*b* (SE)[a]	*b* (SE)	*b* (SE)
% ASP compliance	0.001 (0.001)	0.002 (0.001)	
2015	0.127 (0.031)***	0.174 (0.052)**	
2016	0.110 (0.037)**	0.309 (0.062)***	−0.026 (0.028)
% ASP × 2015[b]		−0.001(0.001)	
% ASP × 2016[c]		−0.003 (0.001)***	
Teaching	−0.315 (0.3)	−0.504 (0.282)	0.261 (0.341)
Bed count	0 (0.001)	0 (0.001)	0 (0.002)
Quality accredited	−0.111 (0.267)	−0.251 (0.232)	0.275 (0.322)
Compliant with CMS requirements	−0.201 (0.16)	−0.241 (0.129)	−0.096 (0.267)
% ICU beds	−0.061 (0.027)*	−0.062 (0.023)**	−0.071 (0.02)***
Length of stay	−0.241 (0.111)*	−0.13 (0.096)	−0.179 (0.104)
Patient safety index	−0.474 (0.141)**	−0.433 (0.151)**	−0.325 (0.168)
% Hospital readmissions	0.066 (0.065)	0.038 (0.06)	−0.01 (0.056)
Lagged % ASP[d]			−0.001 (0.001)
2017			−0.08 (0.044)
Public	−0.714 (0.596)	−0.824 (0.567)	0.985 (0.418)*
Private for profit	0.32 (0.285)	0.258 (0.235)	0.295 (0.655)
Rural	−0.271 (0.387)	−0.252 (0.305)	0.029 (0.374)
Changes in ownership = 1	−1.162 (0.977)	−1.504 (0.896)	0.409 (0.563)
Changes in ownership >1	−3.147 (1.165)**	−3.003 (1.07)**	0.309 (0.9)
Emergency services	0.035 (0.467)	0.035 (0.3)	0.343 (0.345)
ICU services	−0.163 (0.703)	−0.413 (0.772)	1.082 (0.263)***
Constant	3.765 (1.67)*	4.480 (1.632)**	0.417 (1.543)
N	151	151	152
R^2	0.667	0.72	0.803

Note. ASP, Antimicrobial Stewardship Program; CDI, *Clostridioides difficile* infection; SIR, standardized infection ratio; CMS, Centers for Medicare and Medicaid Services; ICU, intensive care unit; SE, standard error.
*$P < .05$; **$P < .01$; ***$P < .001$.
[a]*b* = regression coefficient, the effect of a 1-unit increase in the independent variable on CDI SIR.
[b]Effect of ASP in 2015, relative to 2014.
[c]Effect of ASP in 2016, relative to 2014.
[d]Effect of ASP on CDI in the following year

hospital-acquired pathogens. MRSA rates, for example, are also driven by person-to-person transmission; therefore, screening and infection control efforts (eg, hand hygiene) may be confounding the results.

Second, resistant strains may also take longer and may require higher levels of ASP compliance or specific restriction policies to impact their infection rates in hospitals. Large, nationwide studies reporting an effect of ASP on rates of MRSA or other resistant bacteria were 7–16 years long and were conducted outside the United States.[33,34] A systematic literature review found large variance in resistant microbe outcomes when assessing the impact of interventions to improve antibiotic prescribing.[35] Mixed results are likely explained by the prevalence density of MRSA and the intensity of the intervention in different studies.[34]

As an example of varying ASP interventions, 2 international studies combined antimicrobial stewardship with hand hygiene interventions and detected a decline in several strains of MRSA.[36,37] Our general measure for ASP did not capture that level of granularity or the those infection control efforts included in stewardship activities; thus, we were unable to determine or analyze the effective components of those programs.

This study has several limitations. First, we were able to obtain only 3 years of state-level ASP data, which may have decreased our statistical power in the state-level analyses. Second, we only had access to the percentage of hospitals that reported compliance with all 7 Core Elements, rather than the distribution of each specific element hospitals adopted and specific stewardship activities at the hospital level. Therefore, we could not assess the association of specific core elements with CDI and MRSA rates. Moreover, because we lacked data on stewardship strategies, we had to use a more general measure for ASP, which may not have had enough granularity to reveal its relationship with resistant infections. Additionally, no study has assessed the validity of the NHSN's ASP survey instrument.

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Finally, we were not be able to estimate causal relationships because unmeasured residual confounders may have affected the analyses. For example, patient safety and infection control programs in hospitals could have some overlap with the Core Elements guidelines and could impact resistant infections (especially MRSA) and CDI rates as well, although we somewhat controlled for this factor by using fixed-effects estimation. Furthermore, a small share of the hospitals reporting ASP data to NHSN may not be the same across the years included in this study.

Policy implications

In this study, we have demonstrated a novel approach to estimating the effect of hospital ASP on infection outcomes nationwide and, therefore, important evidence to the incipient body of literature in the field. Perhaps most importantly, our findings suggest that increasing documentation of the 7 core elements may be associated with decreases in CDI SIR in acute-care hospitals. However, even though reported compliance with the Core Elements guidelines has increased in all states nationwide, we did not find evidence of an association with MRSA SIR.

Policy makers can use insights from this study to advocate for comprehensive hospital ASPs. Payers may also use evidence from this study to incorporate ASP-related financial incentives in payment models. In the healthcare setting, administrators can use our results to leverage momentum for the local implementation of all components of hospital ASPs and education of healthcare personnel. Providers may use it for continued education and to increase awareness of the importance of complying with hospital policies to promote the judicious use of antibiotics.

Research on hospital ASPs would greatly benefit from more granular data on the components of ASP and types of stewardship activities, especially if they become available at the hospital level. Researchers should seek mechanisms to make possible or facilitate obtaining such data from governmental health agencies. Because ASP data are available from 2014 onward, future research will also benefit from longer follow-up periods and, possibly, from using other relevant microorganisms in addition to those in this study.

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References

1. Antimicrobial resistance action package. Global Health Security Agenda website. https://ghsagenda.org/home/action-packages/antimicrobial-resistance/.
2. Biggest threats and data. Centers for Disease Control and Prevention website. http://www.cdc.gov/drugresistance/threat-report-2013/index.html. Published 2013. Accessed December 2, 2019.
3. Dellit TH, Owens RC, Mcgowan JE, *et al.* Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007;44:159–177.
4. Fridkin S, Baggs J, Fagan R. Vital signs: improving antibiotic use among hospitalized patients. *Morb Mortal Wkly Rep* 2014;63:194–200.
5. Levin PD, Idrees S, Sprung CL, *et al.* Antimicrobial use in the ICU: indications and accuracy-an observational trial. *J Hosp Med* 2012;7:672–678.
6. Alshammari TM, Larrat EP, Morrill HJ, Caffrey AR, Quilliam BJ, LaPlante KL. Risk of hepatotoxicity associated with fluoroquinolones: a national case-control safety study. *Am J Heal Pharm* 2014;71:37–43.
7. Core elements of hospital antibiotic stewardship programs. Centers for Disease Control and Prevention website. https://www.cdc.gov/antibiotic-use/core-elements/hospital.html. Published 2014. Accessed December 2, 2019.
8. Karanika S, Paudel S, Grigoras C, Kalbasi A, Mylonakis E. Systematic review and meta-analysis of clinical and economic outcomes from the implementation of hospital-based antimicrobial stewardship programs. *Antimicrob Agents Chemother* 2016;60:4840–4852.
9. Morrill HJ, Caffrey AR, Gaitanis MM, Laplante KL. Impact of a prospective audit and feedback antimicrobial stewardship program at a Veterans' Affairs medical center: a six-point assessment. *PLoS One* 2016;11(3):1–20.
10. Khdour MR, Hallak HO, Aldeyab MA, *et al.* Impact of antimicrobial stewardship programme on hospitalized patients at the intensive care unit: a prospective audit and feedback study. *Br J Clin Pharmacol* 2018;84: 708–715.
11. DiazGranados CA. Prospective audit for antimicrobial stewardship in intensive care: impact on resistance and clinical outcomes. *Am J Infect Control* 2012;40:526–529.
12. Schuts EC, Hulscher MEJL, Mouton JW, *et al.* Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. *Lancet Infect Dis* 2016;16:847–856.
13. Kelly AA, Jones MM, Echevarria KL, *et al.* A report of the efforts of the veterans health administration national antimicrobial stewardship initiative. *Infect Control Hosp Epidemiol* 2017;38:513–520.
14. Mijović B, Dubravac-Tanasković M, Račić M, Bojanić J, Stanić S, Lazarević DB. Outcomes of intrahospital antimicrobial stewardship programs related to prevention of clostridium difficile infection outbreaks. *Med Glas* 2018;15:122–131.
15. Antimicrobial stewardship toolkit. The Joint Commission website. https://www.jcrinc.com/antimicrobial-stewardship-toolkit/. Published 2013. Accessed December 2, 2019.
16. Antibiotic resistance patient safety atlas: antibiotic resistance HAI data. Centers for Disease Control and Prevention website. https://gis.cdc.gov/grasp/PSA/MapView.html. Published 2016. Accessed December 2, 2019.
17. Fast facts on US hospitals. American Hospital Association website. https://www.aha.org/statistics/fast-facts-us-hospitals. Published 2019. Accessed December 2, 2019.
18. Hospital Compare. About the data: infections. Centers for Medicare and Medicaid Services website. https://www.medicare.gov/hospitalcompare/Data/Healthcare-Associated-Infections.html. Published 2019. Accessed August 2, 2018.
19. Pollack LA, Santen KL Van, Weiner LM, Dudeck MA, Edwards JR, Srinivasan A. Antibiotic stewardship programs in US acute-care hospitals: findings from the 2014 National Healthcare Safety Network annual hospital survey. *Clin Infect Dis* 2016;63:443–449.
20. Antibiotic stewardship programs vary in US hospitals: CDC survey explores how hospital size, location may influence details. The Pew Charitable Trusts website. https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2016/10/antibiotic-stewardship-programs-vary-in-us-hospitals. Published 2017. Accessed March 7, 2019.
21. FACT SHEET: Obama administration releases national action plan to combat antibiotic-resistant bacteria. The White House website. https://www.whitehouse.gov/the-press-office/2015/03/27/fact-sheet-obama-administration-releases-national-action-plan-combat-ant. Published 2015. Accessed December 2, 2019.
22. Barlam TF, Cosgrove SE, Abbo LM, *et al.* Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis* 2016;62:1197–1202.
23. New antimicrobial stewardship standard. The Joint Commission website. https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf. Published 2016. Accessed December 2, 2019.
24. Pogorzelska-Maziarz M, Herzig CTA, Larson EL, Furuya EY, Perencevich EN, Stone PW. Implementation of antimicrobial stewardship policies in US hospitals: findings from a national survey. *Infect Control Hosp Epidemiol* 2015;36(3):261–264.
25. O'Leary EN, Van Santen KL, Webb AK, Pollock DA, Edwards JR, Srinivasan A. Uptake of antibiotic stewardship programs in US acute-care hospitals:

findings from the 2015 National Healthcare Safety Network annual hospital survey. *Clin Infect Dis* 2017;65(10):1748–1750.

26. Logan A, Williamson J, Reinke E, Jarrett S, Boger M, Davidson L. Establishing an antimicrobial stewardship collaborative across a large, diverse healthcare system. *Jt Comm J Qual Patient Saf* 2019;45:591–599.
27. Talpaert MJ, Rao GG, Cooper BS, Wade P. Impact of guidelines and enhanced antibiotic stewardship on reducing broad-spectrum antibiotic usage and its effect on incidence of *Clostridium difficile* infection. *J Antimicrob Chemother* 2011;66:2168–2174.
28. Christensen A, Barr V, Martin D, *et al.* Diagnostic stewardship of *C. difficile* testing: a quasi-experimental antimicrobial stewardship study. *Infect Control Hosp Epidemiol* 2019;40:269–275.
29. Dantes R, Mu Y, Hicks LA, *et al.* Association between outpatient antibiotic prescribing practices and community-associated *Clostridium difficile* infection. *Open Forum Infect Dis* 2015;2(3):ofv113. doi:10.1093/ofid/ofv113.
30. Sarma JB, Marshall B, Cleeve V, Tate D, Oswald T, Woolfrey S. Effects of fluoroquinolone restriction (from 2007 to 2012) on *Clostridium difficile* infections: interrupted time-series analysis. *J Hosp Infect* 2015;91: 74–80.
31. Elligsen M, Walker SA, Pinto R, *et al.* Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. *Infect Control Hosp Epidemiol* 2012;33: 354–361.
32. Cohen SH, Gerding DN, Johnson S, *et al.* Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol* 2010;31:431–455.
33. Boel J, Andreasen V, Jarløv JO, *et al.* Impact of antibiotic restriction on resistance levels of *Escherichia coli*: a controlled interrupted time series study of a hospital-wide antibiotic stewardship programme. *J Antimicrob Chemother* 2016;71:2047–2051.
34. Lawes T, Lopez-Lozano JM, Nebot CA, *et al.* Effect of a national 4C antibiotic stewardship intervention on the clinical and molecular epidemiology of *Clostridium difficile* infections in a region of Scotland: a non-linear time-series analysis. *Lancet Infect Dis* 2017;17:194–206.
35. Davey P, Marwick CA, Scott CL, *et al.* Interventions to improve antibiotic prescribing practices for hospital inpatients (review). *Cochrane Database Syst Rev* 2017;2:CD003543. doi:10.1002/14651858.cd003543.pub4.
36. Lawes T, López-Lozano JM, Nebot C, *et al.* Turning the tide or riding the waves? Impacts of antibiotic stewardship and infection control on MRSA strain dynamics in a Scottish region over 16 years: non-linear time series analysis. *BMJ Open* 2015;5:e006596. doi:10.1136/bmjopen-2014-006596.
37. Kim YC, Kim MH, Song JE, *et al.* Trend of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia in an institution with a high rate of MRSA after the reinforcement of antibiotic stewardship and hand hygiene. *Am J Infect Control* 2013;41(5):e39–e43.